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Postnatal Atresia of Extraparenchymal Pulmonary Veins, Fulminant Necrotizing Pulmonary Arteritis and Elevated Circulating Immune Complexes

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An infant with operatively corrected total anomalous pulmonary venous connection developed postnatal atresia of the extraparenchymal left pulmonary veins with secondary arteritis of the ipsilateral intraparenchymal pulmonary arteries. Atresia of the right or left main pulmonary veins or of the common pulmonary vein is a rare occurrence and it is believed that association of such with necrotizing pulmonary arteritis has never been reported. This case illustrates the potential consequences of severe pulmonary venous obstruction in the absence of a left to right shunt.

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Patients with pulmonary hypertension due to shunt-related pulmonary vascular obstructive disease may eventually develop necrotizing pulmonary arteritis. We describe an infant with severe necrotizing arteritis secondary to the postnatal evolution of extraparenchymal pulmonary vein atresia. No systemic-pulmonary shunt was present, total anomalous pulmonary venous connection to the coronary sinus having been repaired 9 months before the baby's death. Circulating immune complexes rose dramatically in the infant with the evolution of arteritis, and misleadingly suggested primary immune complex vasculitis as the cause of pulmonary vascular injury. In four previously reported cases of total anomalous pulmonary venous connection and concurrent pulmonary vein atresia (1–4), pulmonary artery obstructive disease was observed; however, necrotizing arteritis was not.

Case Report

An 11 month old white male infant had presented with dyspneic episodes and excessive diaphoresis at birth. At 2 months of age increasing diaphoresis, tachypnea, cardiomegaly and a heart murmur led to his referral to our medical center for evaluation.

Clinical features. The baby was pale, dyspneic, cyanotic and in slight distress. Respiratory rate was 60/min and heart rate 172 beats/min. The lungs were clear. A grade 2/6 systolic ejection murmur was heard at the upper right sternal border. Chest roentgenograms revealed significant cardiomegaly and pulmonary artery dilation. Echocardiography revealed a very dilated and hypertrophied right ventricle and enlarged right atrium. Left atrial and ventricular dimensions were small. Cardiac catheterization at 2 months of age further revealed an atrial septal defect, total anomalous pulmonary venous connection to the right atrium by way of the coronary sinus and pulmonary hypertension (Table 1). Pulmonary to systemic flow (Qp/Qs) was approximately 5.7:1. The left pulmonary veins were narrow but patent (Fig. 1A). Significant gradients existed from the left lower pulmonary vein to the main common venous chamber (coronary sinus) (mean 7 mm Hg), as well as at the entrance of the common venous chamber to the right atrium (mean 12 mm Hg). Correspondingly, cineangiograms revealed mild "wasting" at the junction of the left lower pulmonary vein with the common pulmonary venous chamber. No discrete areas of stenosis were present. Intracardiac repair of the total anomalous pulmonary venous connection and the atrial septal defect was performed to relieve the systemic-suprasystemic right-sided pressures. All pulmonary veins were patent at operation.

Clinical course. After initial improvement in the infant's condition, over a period of 8 months pulmonary hyperten-

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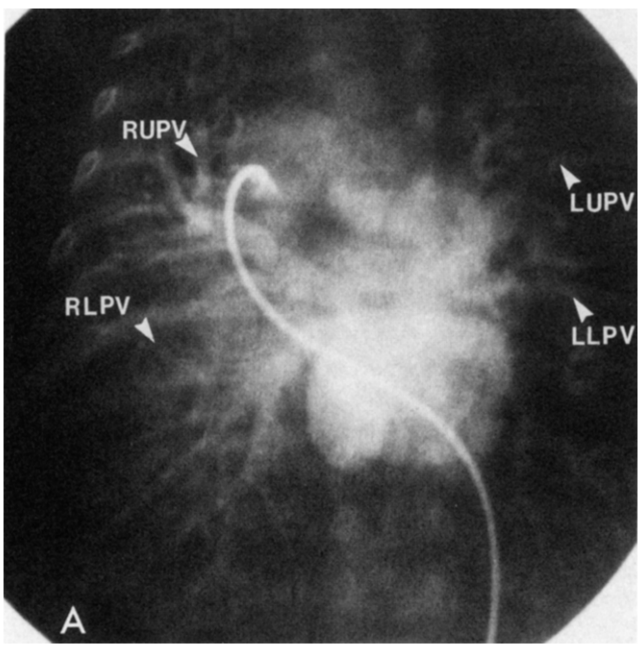
Table 1. Hemodynamic and Oxygenation Data

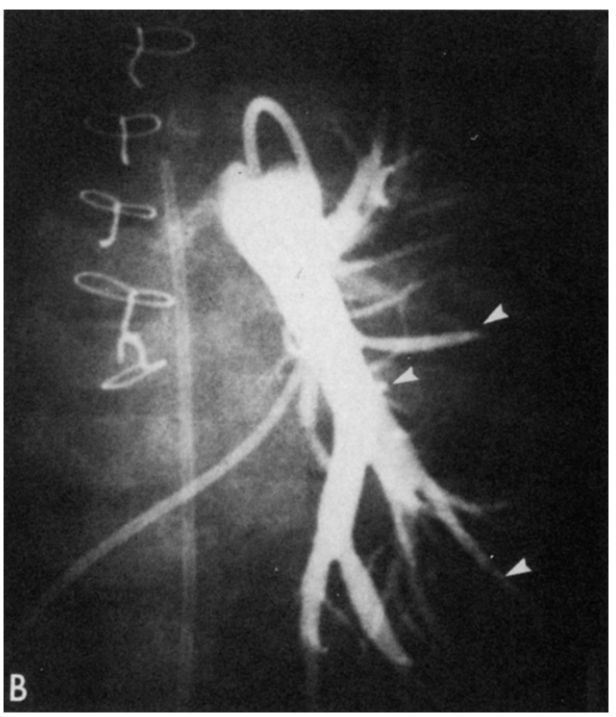
Site	At Age 2 Months		At Age 10 Months	
	O_2 Sat (%)	Pressure (mm Hg)	O_2 Sat (%)	Pressure (mm Hg)
SVC	41	—	47	—
HRA	81	—	49	—
LRA	76	(6)	49	(7)
IVC	72	—	51	—
RV	88	90/0 (11)	47	90/10
LPA	85	90/35 (58)	47	90/40 (60)
RPA	86	90/35 (56)	47	90/40 (60)
LLPV	92	—	Atretic	Atretic
LA	77	(5)	—	—
LV	79	70/0 (8)	97	100/6 (75)
Fem A	81	75/42 (54)	—	100/55 (75)

Mean pressures are in parentheses. Fem A = femoral artery; HRA = high right atrium; IVC = inferior vena cava; LA = left atrium; LLPV = left lower pulmonary vein; LPA = left pulmonary artery; LRA = lower right atrium; LV = left ventricle; RPA = right pulmonary artery; RV = right ventricle; Sat = saturation; SVC = superior vena cava.

sion recurred with progressive, episodic right heart failure. On readmission, he had a respiratory rate of 60/min and a heart rate of 90 beats/min. Breath sounds were coarse. Cardiac catheterization at 10 months of age revealed obstruction (lack of flow) in the left pulmonary veins in association with marked pulmonary hypertension (mean pulmonary artery pressure 75 mm Hg) (Table 1). As well, angiograms of the left pulmonary arteries revealed numerous attenuated and abruptly blocked arteries (Fig. 1B). The Qp/Qs ratio was 1:1. Surgery was recommended to attempt repair of the left pulmonary veins (suspected to be abnormal because of the previous total anomalous pulmonary venous connection repair); however, at operation, atresia of the left pulmonary veins was found and a left pneumonectomy was performed.

Figure 1. Angiography. **A,** Cardiac angiogram at 2 months of age with levophase showing total anomalous pulmonary connection to the right atrium. Left pulmonary veins are narrow but patent. LLPV = left lower pulmonary vein; LUPV = left upper pulmonary vein; RLPV = right lower pulmonary vein; RUPV = right upper pulmonary vein. **B,** Pulmonary artery angiogram at 10 months of age showing proximal dilation, and distal attenuation and obstruction (**white arrowheads**) with diminished segmental arterial branches in the distal left pulmonary artery system.





Morphologic findings. The extraparenchymal left pulmonary veins were occluded by a fibromuscular thickening

of the vessel walls, the interface between intima and media being effaced (Fig. 2). No inflammation was present in these or any other pulmonary veins. The interlobular veins were normal.

A striking, necrotizing, fibrinoid destruction of many medium (100 to 1,000 μm in diameter) and small (<100 μm in diameter) pulmonary arteries of the left lung was associated with multiple pulmonary artery occlusions by thrombic material. The arterial lesions varied in age from acutely necrotic to healing and recanalized (Fig. 3). Numerous polymorphonuclear leukocytes and infrequent mononuclear cells and eosinophils were present in the necrotic vessel walls. No organisms were present by histologic stains or on microbiologic culture. Other features of plexigenic pulmonary arteriopathy were absent. No parenchymal infarcts were present, although periarterial hemorrhages were multifocal. Subpleural and interlobular lymphatics were dilated. A diffuse bronchitis and broncheolitis with mononuclear cell infiltration of the lamina propria was noted in association with peribronchial follicular lymphoid hyperplasia. Numerous aggregates of alveolar macrophages were also present.

Circulating immune complexes. Concurrent with the left pneumonectomy, peripheral blood quantitation of circulating immune complexes (5) revealed a dramatic elevation in both immunoglobulins IgG (250 μg/ml; normal <30) and IgM (326 μg/ml; normal <30) complexes. Although initial consideration was given to systemic immune complex vasculitis as a cause of the necrotizing pulmonary arteriopathy, the patient had no evidence of similar morphologic (or functional) sequelae in any other organ including the right lung. Thus, it became clear that the immune complexes were secondary to the profound pulmonary venous hypertension-related pulmonary artery necrosis. At the time of the patient's terminal admission 1 month later, his condition had markedly improved, and IgG and IgM immune complex levels had fallen to 108 and 131 μg/ml, respectively. The infant developed an acute gastrointestinal viral-like syndrome, with apnea and cyanosis and preterminal complete heart block. A complete autopsy was permitted.

Autopsy findings. Dense gelatinous adhesions were present on the epicardial and right pleural surfaces. As well, the right pleural cavity contained 80 cc of serosanguinous fluid. The operative resection margin of the absent left lung was well healed. Although the right lung was diffusely congested, no vascular obstruction was present, and specifically the hilar pulmonary veins were thin-walled and patent. Microscopically, moderate medial and intimal thickening of small and medium-sized intraacinar pulmonary arteries was present. No arteritis was present. Extensive aggregates of alveolar macrophages were noted. The pulmonary trunk was considerably dilated (1.7 cm diameter) compared with the aorta (0.9 cm diameter) and was associated with marked right ventricular hypertrophy with numerous subendocardial scars in the right ventricular free wall myocardium. Multiple intussusceptions were present in the small bowel in association with hyperplastic lymphoid foci, and an enzyme-linked immunosorbentassay (ELISA) for rotovirus on postmortem stool was positive. The gastrointestinal infection with associated intussusceptions and with concurrent desquamative interstitial pneumonitis led to the baby's death.

Discussion

Obstruction of pulmonary venous flow is a common and significant problem in patients with total anomalous pulmonary venous connection (6). Specifically, obstruction may be due to extravascular compression of veins that take a

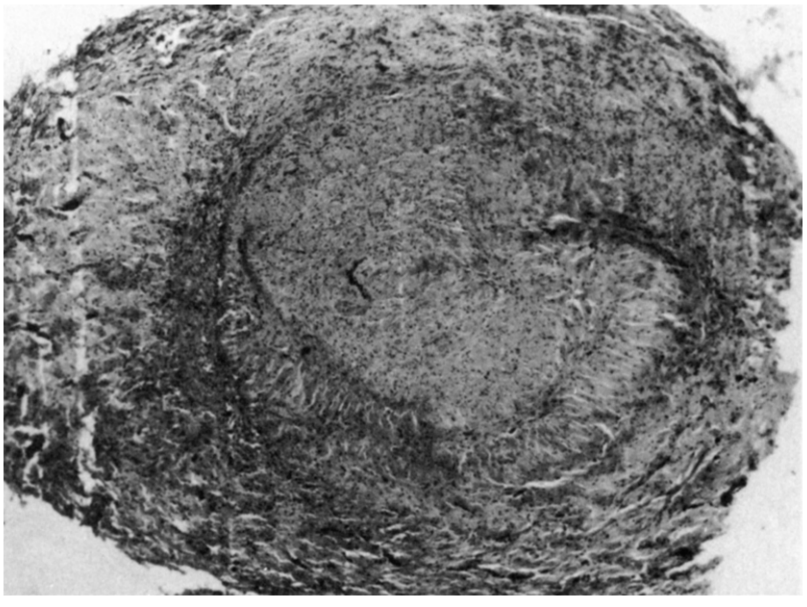


Figure 2. Photomicrograph of an extraparenchymal segment of the left pulmonary vein. Occlusion by fibromuscular thickening and dysplasia of the intima and media is evident. Hematoxylin-eosin stain; original magnification ×33, reduced by 28%.

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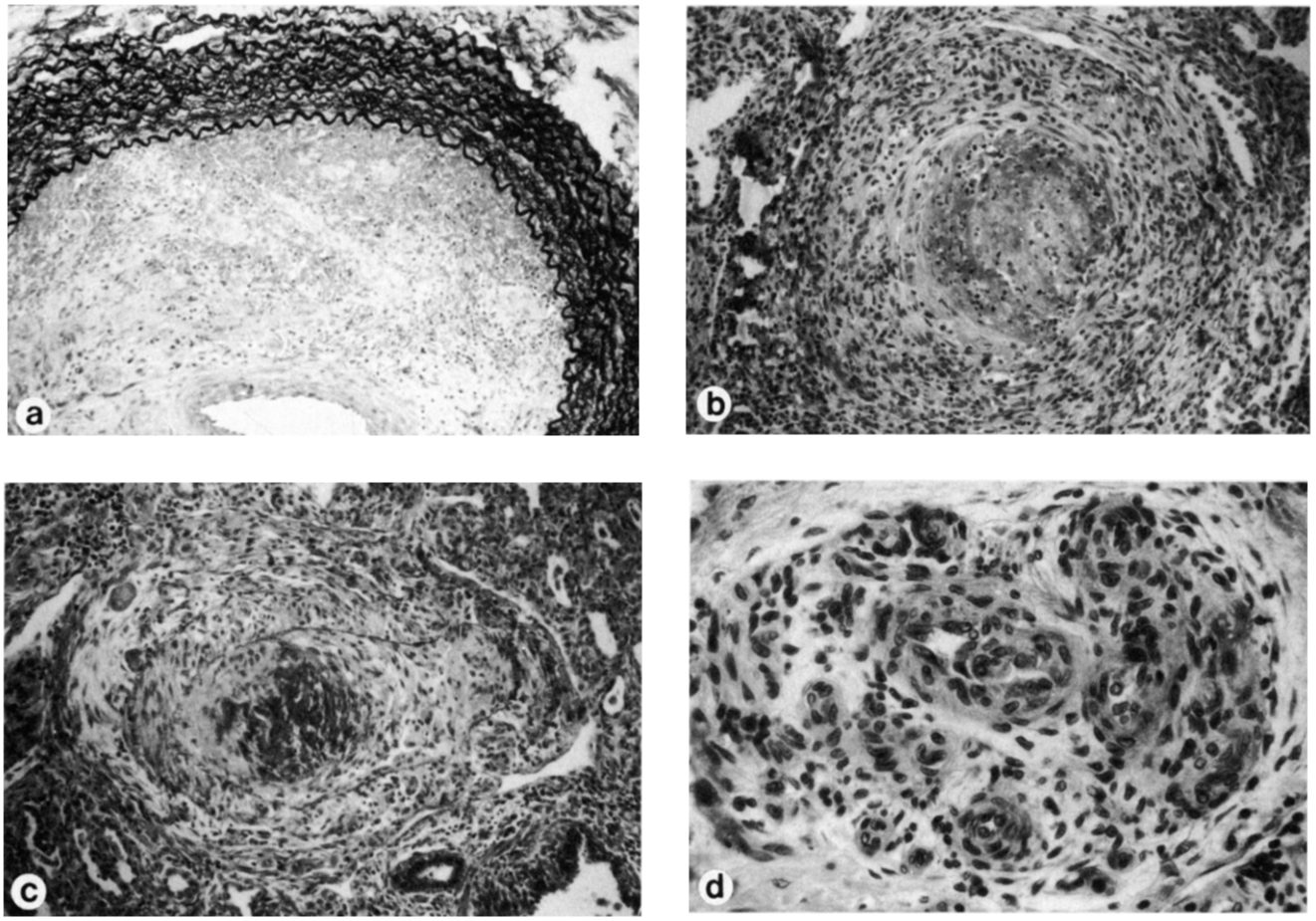

Figure 3. Photomicrographs at autopsy of representative sections from pulmonary arteries illustrating the thrombotic impact and temporal progression of healing, necrotizing arteritis. **a,** Healed thrombotic near-occlusion with fibrous intimal healing in an elastic pulmonary artery. **b,** Necrotizing, fibrinoid destruction of a muscular pulmonary artery. **c,** Fibrinoid necrosis of a muscular pulmonary artery with evidence of peripheral healing. **d,** Recanalized muscular pulmonary artery. Movat pentachrome stains, original magnification ×125 (**a**), ×333 (**b** and **c**) and ×500 (**d**), all reduced by 28%.

long course from the hilum of the lungs to the systemic veins or the heart itself. However, there is a separate group of patients with extraparenchymal pulmonary vein stenosis or atresia, or both, who have luminal compromise due to intrinsic abnormalities of the venous vessels themselves. Association of such pulmonary vein narrowing with total or partial anomalous pulmonary venous connection is appreciated (7); however, the number of pediatric patients with frank unilateral or common pulmonary vein atresia is few (Table 2). It is this latter group of patients which is most similar to our patient.

Unilateral pulmonary vein atresia. Since 1974, 13 patients, including our own with unilateral pulmonary vein atresia have been reported on (3,4,8–11) (Table 2). Of these 13 patients, 9 were male and 4 were female. They presented clinically as early as 1 day of age and as late as 10 years. Their outcome was variable, four patients having died at ≤3 years, the remainder being alive at the time of the respective reports. Although cyanosis and tachypnea were the most common symptoms or signs, other less specific symptoms were also observed. Most commonly the patients had no other associated cardiac lesions (seven patients), although two had an atrial septal defect and one had a ventricular septal defect and a patent ductus arteriosus. Only two patients, excluding our own, had anomalous pulmonary venous connection associated with the atretic veins, both of these being of the partial type. The left pulmonary veins were involved in nine patients as compared with right pulmonary veins in four. A single patient had total anomalous pulmonary venous connection with pulmonary veins connecting to the coronary sinus.

Common pulmonary vein atresia. When newborns with common pulmonary vein atresia are considered, the number of patients reported on is similar to that for unilateral vein atresia, 17 in all being reported in 10 studies since 1968 (1,2,12–19). When sex was known, maleness predominated (six patients versus three), which was similar to the sex ratio in unilateral pulmonary vein atresia. Not unexpectedly, pa-

Table 2. Reports of Pediatric Patients With Unilateral Pulmonary Vein Atresia

Reference				Outcome			Associated Cardiac Lesions	Atretic Pulmonary Veins	
First Author	Date	Sex	Age at Presentation	Death	Age at Death	Symptoms/Signs		R	L
Sade (8)	1974	F	5 Mo*·†	+	10 Mo	Pulmonary infections Failure to thrive	0	0	+
Beerman (9)	1983	F	120 Mo*	0	—	Chest pain	0	+	0
		M	48 Mo*·†	0	—	Mild clubbing; mild activity intolerance	VSD; PDA	0	+
		M	66 Mo*·†	0	—	Hemoptysis	0	0	+
Samanek (3)	1974	M	1 Mo*	+	7 Wk	Cyanosis; tachypnea	PAPVC§	+	0
Nasrallah (10)	1975	M	16 Mo*·†	0	—	Right pleural effusion	0	+	0
Swischuk (11)	1980	M	30 Mo*·†	0	—	Congestive heart failure	0	0	+
		F	24 Mo*	‡		Hemoptysis		+	0
		M	30 Mo*·†	0	—	Cyanosis; hemoptysis	0	0	+
Kingston (4)	1983	M	14 Mo*·†	0	—	Hemoptysis	0	0	+
		M	1 Day*·†	+	36 Mo	Cyanosis	PAPVC‖	0	+
		F	4 Days*·†	0	—	Cyanosis	ASD	0	+
Kelley (this article)	1987	M	2 Mo*·†	+	11 Mo	Dyspnea; diaphoresis	ASD; TAPVC#	0	+
Total		9M;4F	4/12				5/13	4/13	9/13
Mean			27.4 Mo		14.8 Mo				

*Catheterization; †operation; ‡incomplete information; §left pulmonary veins to portal vein; ‖right upper lobe veins to superior vena cava; #all pulmonary veins to the coronary sinus. ASD = atrial septal defect; F = female; M = male; PAPVC = partial anomalous pulmonary venous connection; PDA = patent ductus arteriosus; TAPVC = total anomalous pulmonary venous connection; VSD = ventricular septal defect.

tients with common pulmonary vein atresia presented at birth or shortly thereafter with a common symptom complex dominated by tachypnea and dyspnea with cyanosis. All but one of the patients reviewed had died, the oldest having lived for only 28 days. Most of the patients had a patent foramen ovale (7 patients), atrial septal defect (3 patients) or patent ductus arteriosus, or both (10 patients). A single patient had pulmonary valve atresia associated with atrial septal defect and patent ductus arteriosus. Again, anomalous pulmonary venous connection was extremely rare (2 of the 17 patients).

Association with anomalous pulmonary venous connection. Our patient has characteristics similar to those of pediatric patients previously reported on with unilateral pulmonary vein atresia. Considering his cardiovascular condition only, after the infant's left pneumectomy, he had done extremely well and might have progressed very favorably had his enteric illness not arisen. It is striking that in considering all pediatric patients with unilateral pulmonary vein atresia (atresia presumed present from birth) and newborns with common pulmonary vein atresia, total anomalous pulmonary venous connection is rare (3 of 30 patients, 10%), and partial anomalous venous connection is even rarer. This is unlike the high frequency of association between extraparenchymal vein stenosis and anomalous pulmonary venous connections. The implication of these observations is uncertain; however, they may reflect the fact that the extraparenchymal pulmonary veins are inherently abnormal, but satisfactorily patent, in many young patients. As time passes in the postnatal period, the evolution of pulmonary vein stenosis may ensue with symptoms presenting at various ages depending on the degree and sites of stenosis. The variable course of progressive stenosis may indeed explain the apparently different subsets of patients we have discussed. Patients with pulmonary vein atresia have a marked intrinsic abnormality of the extraparenchymal veins unrelated to their cardiac connection, owing to a late embryologic mistake (1). Patients who present later may have less severe structural abnormalities of the veins, which are embryogenically linked to persistence of splanchnic-systemic venous connections and the resultant aberrant venocardiac connection.

Pulmonary vascular injury in pulmonary venous obstruction. The impact of severe pulmonary venous obstruction on the pulmonary arteries must be separated from the impact of coexistent total anomalous pulmonary venous connection with a left to right shunt (20). Necrotizing arteritis has not been described with or without partial or total anomalous pulmonary venous connections. The present patient illustrates the potential severity of pulmonary venous hypertension in the absence of a shunt. As well, in our patient, the parallel between circulating immune complex levels and the severity of pulmonary vascular injury is documented. With further patient comparisons and more selective and sensitive immune complex assays, circulating immune complex levels may become a useful measurement in the eval-

uation of vascular injury due to pulmonary hypertension from any cause.

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